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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,873	09/05/2003	Michael S. Kopreski	00-1312-K	5207

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,873	KOPRESKI, MICHAEL S.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,16-23,25,27-34,45,46,49 and 50* is/are pending in the application.

4a) Of the above claim(s) *3,7,10,11,19,21,22,30-34,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9,12,14,16-18,20,23,25,27-29,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 in the reply filed on November 13, 2007 is acknowledged. The traversal is on the ground(s) that "[A]pplicant respectfully traverses the newly-imposed restriction on the grounds that prosecution of the pending claims is sufficiently far advanced that completing examination of the two claims grouped outside the claimed group identified by the Examiner would occasion no undue burden on the Office".

The above arguments have been fully considered and have not been found persuasive toward the withdrawal of the restriction requirement nor persuasive toward the relaxation of same such that Groups I and II will be examined together because there is a burden on the examiner to search Groups I and II together. For example, the search required for Group I such as detecting, inferring, or monitoring a neoplastic disease in a human in claim 1 is not required for Group II while the search required for Group II such as comparing an amount or concentration of a housekeeping gene RNA from blood plasma or serum to an amount or concentration of a tumor-associated RNA from blood plasma or serum of a human in claim 31 is not required for Group I. Therefore, The requirement is still deemed proper and is therefore made FINAL. Claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 will be examined.

Claim Objections

2. Claim 1 or 5 or 9 or 20 is objected to because of the following informality: "a neoplastic disease is detected, inferred or monitored in a human" in "wherein" phrase should be "the neoplastic disease is detected, inferred or monitored in the human".

3. Claim 9 or 20 is objected to because of the following informalities: (1) "a define reference range RNA" in "wherein" phrase should be "the reference range RNA"; and (2) "a human group or population" in "wherein" phrase should be "the defined human group or population".

4. Claim 20 is objected to because of the following informality: "plasma or serum" in line 12 should be "non-cellular fraction".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Scope of enablement

Claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a product amplified from total extracellular RNA from plasma or serum of a human, does not reasonably provide enablement for detecting, inferring, or monitoring any kind of neoplastic disease in a human using the methods recited in claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detecting, inferring or monitoring a neoplastic disease in a human. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 encompass a method of detecting, inferring or monitoring any kind of neoplastic disease in a human by detecting one or more RNA that expressed or overexpressed in the neoplastic disease in plasma or serum or a non-cellular fraction of blood wherein the neoplastic disease is detected, inferred or monitored in the human when the amplified product or signal of the one or more RNA expressed or overexpressed in said neoplastic disease, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a human, is detected in an amount or concentration greater than a reference amount or concentration for said RNA or cDNA therefrom determined from

plasma or serum or a non-cellular fraction of blood from a human group or population without said neoplastic disease.

Working Examples

The specification provides working examples (see pages 24-26) for detecting tyrosinase RNA in serum from normal human and a human with malignant melanoma and for detecting c-abl RNA in serum from human.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification teaches to detect tyrosinase RNA in serum from normal human and a human with malignant melanoma and detect c-abl RNA in serum from human (see the specification, pages 24-26), the specification does not provide a guidance to show that detection one or more RNA that expressed or overexpressed in a neoplastic disease in plasma or serum or a non-cellular fraction of blood can be used for detecting, inferring or monitoring the neoplastic disease in a human. Furthermore, there is no experimental data in the specification to support the claimed invention. During the process of the prior art search, the examiner has not found any prior art which is related to claimed invention.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether detection one or more RNA that expressed or overexpressed in a neoplastic disease in plasma or serum or a non-cellular fraction of blood can

be used for detecting, inferring or monitoring the neoplastic disease in a human. Furthermore, there is no experimental data in the specification to support the claimed invention. First, since the claims do not require that neoplastic disease is a specific cancer and it is known that 5T4 is highly expressed in both breast and lung cancers (see Table II in page 92 from Southall et al., Br. J. Cancer, 61, 89-95, 1990) and 5T4 mRNA can be detected in both breast and lung cancer patient serum (see page 172, abstract from Kopreski et al., Annals of the New York Academy of Science, 945, 172-178, 2001), when the amplified product or signal of 5T4 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a woman, is detected in an amount or concentration greater than a reference amount or concentration for 5T4 mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a human group or population without said neoplastic disease, based on above experimental results, it is unclear how a skilled artisan can determine that the woman is a human with breast caner and is not a human with lung cancer or the woman is a human with lung caner and is not a human with breast cancer. Second, since it is known that hnRNP-A2/B1 is highly expressed in pancreatic tissues from smokers and pancreatic adenocarcinomas (see page 215, abstract from Yan-Sanders et al., Cancer Letters, 183, 215-220, 2002), when the amplified product or signal of hnRNP-A2/B1 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a human, is detected in an amount or concentration greater than a reference amount or concentration for hnRNP-A2/B1 mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a non-smoking human group or population without said neoplastic disease, based on above experimental results, it is unclear how a skilled artisan can determine that the human is a human with pancreatic adenocarcinomas and is not a

smoking human or the human is a smoking human and is not a human with pancreatic adenocarcinomas. Third, since total extracellualr RNA in plasma or serum is a RNA mixture which contains a lot of different RNAs, it is unclear how to detect, infer or monitor a neoplastic disease in a human by comparing the amount or concentration or comparative value of one or more RNA expressed or overexpressed in said neoplastic disease in plasma or serum or a non-cellular fraction of blood with a reference range total extracellular RNA amount, concentration, or value determined from a human group or population as recited in claims 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46.

With above unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the methods recited in claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 can be used for detecting, inferring, or monitoring any kind of neoplastic disease in a human.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1 or 5 is rejected as vague and indefinite because it is unclear that a human group or population in step c) is identical to a human group or population without said neoplastic disease in "wherein" phrase or not. Please clarify.

10. Claim 9 or 20 is rejected as vague and indefinite because it is unclear that a reference range RNA is identical to one or more tumor-associated human RNA species or not. Please clarify.

11. Claim 12 or 14 recites the limitation "the group or population with a neoplastic disease" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no phrase "group or population with a neoplastic disease" in claim 9. Please clarify.

12. Claim 23 or 25 recites the limitation "the group or population with a neoplastic disease" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no phrase "group or population with a neoplastic disease" in claim 20. Please clarify.

Response to Arguments

13. Applicant's arguments with respect to claims 1, 2, 4-6, 8, 9, 12, 14, 16-18, 20, 23, 25, 27-29, 45, and 46 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

14. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

January 16, 2008

FRANK LU
PRIMARY EXAMINER